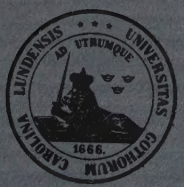
Bulletin No. 39 from the Department of Surgery,

University of Lund, S-221 85 LUND

1983

ALCOHOL AND TRAUMA

Effects of alcohol on microaggregate formation, platelet aggregation and function, traumatic shock and outcome of trauma, an experimental and clinical study



Olle Elmér

From the Department of Surgery, University of Lund,

S-221 85 LUND, Sweden

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Effects of alcohol on microaggregate formation, platelet aggregation and function, traumatic shock and outcome of trauma, an experimental and clinical study

by

Olle Elmér

Lund 1983

The present thesis is based on the following papers:

I. Elmér O, Göransson G, Saku M and Bengmark S: Ethanol-induced microaggregate formation in pig and rabbit blood. An in vitro study.
Thromb Hemost 37:344-350, 1977.

II. Bengmark S, Elmér O and Göransson G: Circulating microaggregates after gastric administration of ethanol in the pig.
Eur Surg Res 12:333-342, 1980.

III. Elmér O, Göransson G, Zoucas E and Bengmark S: Effects of ethanol on platelet aggregation. An in vitro study.
Res Exp Med, 1983, in press.

IV. Elmér O, Bengmark S, Göransson G, Sundqvist K and Söderström N: Acute portal hypertension after gastric administration of ethanol in the pig.
Eur Surg Res 14:298-308, 1982.

V. Elmér O, Göransson G and Molander N: Effect of acute and chronic ethanol intake on metastasis formation in rat liver.
J Surg Oncol 12:357-363, 1979.

VI. Elmér O, Göransson G and Zoucas E: Impairment of primary hemostasis after alcohol ingestion in man due to platelet dysfunction.
Submitted for publication 1983.

VII. Elmér O, Gustafsson I, Göransson G and Thomsson D: Acute alcohol intoxication and traumatic shock. An experimental study on circulating microaggregates and survival.
Eur Surg Res 1983, in press.

VIII. Elmér O and Lim RC: Effects of acute alcohol ingestion on outcome of non-neurologic trauma.
Submitted for publication 1983.

In the text the above articles are referred to by their Roman numerals.

Equivalence of units used in measuring concentration of alcohol

Per cent (%) g/dl	Per mille (‰) mg/ml	mg/100 ml (mg %) mg/dl	mM
0.001	0.01	1	0.217
0.01	0.1	10	2.17
0.1	1.0	100	21.7
1.0	10.0	1 000	217

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INTRODUCTION

Until after World War II, the surgery of trauma was a central area of surgical practice. Then the technical and physiological advances encouraged a diversification of surgery into highly specialized fields, far removed from trauma. The advances in the care of critically injured was mainly done by military medical personnel during World War II and further refined during the Korean and Vietnam conflicts. These experiences gave deeper understanding of traumatic shock, the necessity for immediate treatment, rapid transportation and the benefits of a team approach to the treatment of injured. By adopting these principles, rescue personnel has received a better training. Rescue vehicles have been better equipped and respond quicker and more adequately thanks to central dispatch and radio communication between rescue personnel at the scene of injury and hospital physicians. As a result, more salvageable patients are now brought to the hospitals than 15 years ago, but the hospital care of the acutely injured patient has regrettably not improved commensurately (1). Improvements are supposed to have been done by means of a more aggressive attitude towards the injured patient. Abdominal lavage for early detection of intra-abdominal bleeding is now performed in most emergency rooms (2), acute thoracotomy saves some patients who would otherwise die (3), and in some settings, mortality has been reduced by directly transferring severely injured to the operating room (4). The number of "unnecessary" trauma deaths has been reduced by regionalization of definitive trauma care to specialized trauma centers (5). Despite these improvements, trauma is still the major cause of death and disability, in industrialized countries, for people between 1-34 years of age. For the whole population, death from trauma is only exceeded by deaths from cardiovascular disease and cancer (6). To improve the care of the injured is therefore a challenge to the whole society.

For the patient who survives the trauma, sepsis and multiorgan failure is the leading cause of mortality (7). Despite the development of sophisticated antibiotics, the mortality from sepsis has not changed significantly (8). Interest has therefore been focused on principles of host defense and immune mechanisms. In a recent study, 80 % of injured patients were found to have an impaired host defense within two hours of the trauma. This state of anergy was later restored while the nutritional status was worsening (9). This indicates that anergy is the result of trauma and stress per se rather than malnutrition. This concept is also supported by the observation in surgical patients that anergy is reversed by reducing stressful events such as control of bleeding and drainage of septic focuses (10). Reticuloendothelial (RE) function is depressed after trauma, by a deficiency in opsonic fibronectin (11), which decreases the resistance to infection (12). Measures should therefore be taken to avoid challenge of the immune system. This can be done by immediate stabilization of fractures, avoiding bacterial contamination, removal of necrotic tissue and drainage of abscesses. Infusion of particulate matters should also be

avoided by limiting the amounts of debris infused with banked blood (13) and blood volume should be restored with crystalloids rather than with albumin solutions (14-17). Gelatin solutions should also be avoided as they might affect platelet function (18). Oxygen should be administered as soon as possible after trauma as a lack of oxygen interferes with wound healing and impairs the intracellular killing mechanisms of phagocytes (19). These measures and maintenance of caloric and protein intake are probably the most important adjuncts to prevent post-traumatic sepsis and multiorgan failure.

Other ways to improve trauma care are preventive measures and to identify external risk factors which can affect the injured. One such factor is acute alcohol intoxication. There exists a strong correlation between alcohol use and trauma as documented for suicide (20), homicide (21), traffic accidents (22, 23), burns (24, 25), drowning (26), and other accidents (27, 28). Despite these facts, surprisingly little attention in the surgical literature has been given to acute alcohol intoxication and trauma care. There are, however, reports which indicate that alcohol intoxication might affect the outcome of trauma. These studies will be discussed.

Alcohol and injuries to the central nervous system

Most studies on alcohol and trauma deal with injuries to the CNS. In a consecutive series of patients with head injuries, more than half of the patients had positive blood alcohol tests (29). In observation of head injuries, nothing is more important than monitoring the level of consciousness, which also may be used as a prognostic factor (30). To assume that alcohol is the only cause for neurologic signs may be misleading and dangerous (31). Only at a blood alcohol level of less than 200 mg/dl can alterations in the consious state not be attributed to intoxication (29). The degree of intoxication can be judged by blood alcohol determinations or estimated from serum osmolality (32), while clinical judgments often are misleading (33, 34). Acute intoxication can per se be detrimental to the CNS. In severely injured patients with high alcohol levels, the brain cells may, during infusion of i.v. fluids, take up too much water through osmosis and deteriorate the condition of the patient (35). Acute alcohol intoxication also reduces man's resistance to cerebral hypoxia (36). In a recent experimental study, it was shown that spinal cord injury, by an unknown mechanism, is potentiated by alcohol (37). This emphasizes the need for alcohol determinations in trauma patients. When the alcohol level is known, it can be calculated to decrease with a rate of approximately 15 mg/dl/hr. Although zero-order kinetics are inappropriate for describing the elimination of alcohol in humans (38), this formula can be used in clinical practice. A recent study indicates that the elimination rate might be increased to 20-24 mg/dl/hr following traumatic shock (39).

Alcohol and resistance to infection

Traumatic wounds are contaminated and the patients' defense mechanisms serve to control infection. Some of these mechanisms are affected by acute alcohol intoxication. Animals inoculated with bacteria develop an inflammatory exsudate that controls infection locally, while intoxicated animals deliver few neutrophils to the infected focus resulting in a spread of bacteria to the blood stream and death from overwhelming infection (40). This decrease in neutrophil mobilization has later been confirmed, using a skin window technique, in acutely intoxicated human volunteers (41). No decrease in the ability to ingest or kill ingested bacteria was found. The mechanism for the poor neutrophil delivery, is probably a decreased neutrophil adherence. Neutrophils must adhere to the endothelium before diapedesis into the tissues (42). Alcohol also reduces adherence in rabbit alveolar macrophages (43). The importance of a normal neutrophil function for protection against bacteremia has recently been documented in humans (44). It should be noted, however, that these effects of alcohol are reversible. Other negative effects of alcohol on host defense are a decreased complement activity, demonstrated in dogs (45), and a reduced bactericidal activity of human serum (46). Alcohol ingestion also depresses RE function, as determined by a reduced clearance of microaggregated albumin, in the rat (47). Another interesting finding is the recent demonstration of increased gastrointestinal permeability following alcohol ingestion (48). One may speculate if this might facilitate the absorption of endogenous toxic metabolites, free radicals and infectious organisms from the gastrointestinal tract causing deleterious effects to the liver and other organs. Although the increased susceptability of alcoholics to infections is well known, it is not possible to predict the result of these impairments of host defense mechanisms by alcohol in the non-alcoholic. It seems reasonable, however, to assume that these negative effects of alcohol, together with the RE depression resulting from the trauma itself (49) and the fact that hemorrhagic shock predisposes to infection (50), will further increase the risk of infection in the intoxicated trauma victim.

Alcohol and hemodynamics

Alcohol has been demonstrated to either decrease (51) or increase (52) coronary blood flow. The conflicting results are probably due to different techniques and alcohol levels employed and the fact that alcohol and its metabolite acetaldehyde have dissimilar hemodynamic effects. In dogs, alcohol is an acute myocardial depressant while acetaldehyde improves cardiac function as a consequence of its vasodilating properties and indirectly as a result of its catecholamine releasing effect (53). The net result, however, is a negative inotropic and chronotropic effect on the heart, which can be potentiated by exercise (54). Ingestion of low to moderate amounts of alcohol has been demonstrated to depress myocardial function in humans (55). In another study, this effect of alcohol could only be

demonstrated after autonomic blockade, which indicates that the negative effects of low or moderate amounts of alcohol on myocardial function might be masked by catecholamine and/or autonomic nervous system discharge (56). A cardiodepressant effect of alcohol is a probable explanation to the increased mortality seen after blunt chest trauma in alcohol intoxicated dogs and rats (57, 58) and may explain the hypotension and bradycardia observed in alcohol intoxicated patients with minor trauma (59). Even when the cardiodepressant effects of alcohol are masked by catecholamine release, they might be evident when general anesthesia is applied for emergency surgical intervention.

Alcohol and blood loss

Intoxicated humans tolerate blood loss poorly compared to other patients (60) and profound hypotension has been described in acutely intoxicated patients after minor trauma (59, 61). The diagnosis of intra-abdominal bleeding after blunt trauma is difficult in the alcohol intoxicated patient who may be uncooperative and has a reduced response to pain. To judge blood loss from hemoglobin, hematocrit or pulse rate is uncertain because alcohol during resorption inhibits the release of antidiuretic hormone (62) resulting in hemoconcentration and because of the negative chronotropic effect of alcohol on the heart (54). Even though the usefulness of abdominal lavage seems overrated, it might be indicated in intoxicated patients where the physical signs are less reliable. In these patients, it is recommended that the lavage catheter is passed through the peritoneum under direct vision (63). The acute blood loss necessary to reduce blood pressure to 60 mmHg in anesthetized dogs pre-treated with alcohol is 2/3 of the volume required in non-intoxicated dogs (64). In another study, a 35 % reduction of blood volume resulted in metabolic acidosis, which the intoxicated dogs were unable to compensate for, and a 30 % mortality while no non-intoxicated dog died (65). These findings have been confirmed in experiments with awake dogs (66). In one study, no hemodynamic changes were found in intoxicated dogs after hemorrhagic shock (67). These findings were, however, probably due to rapid removal and reinfusion of blood and the fact that shock was only maintained for one minute.

Alcohol and metabolism

The likely effects of acute alcohol intoxication and trauma on acid-base balance is a combined metabolic and respiratory acidosis. Ninety per cent of absorbed alcohol is oxidized, principally in the liver, to acetaldehyde and then to acetate. Oxidation is catalyzed by the enzymes alcohol- and aldehyde-dehydrogenase, both enzymes require nicotinamide adenin dinucleotide (NAD) as hydrogen acceptor. The enhanced NADH/NAD ratio then reflects itself, in an increased lactate/pyrouvate ratio, which results in hyperlactacidemia because of both decreased utilization and enhanced production of lactate by the liver (68). The low-flow state associated with hemorrhagic shock also

results in metabolic acidosis, but is normally compensated for by an increased ventilation. In the intoxicated trauma patient, this might be inhibited by the depressant effect of alcohol upon respiration (65) thereby permitting a progressive acidosis. Acidosis is also a common feature in accidental hypothermia which easily can develop in alcohol intoxicated trauma victims. Alcohol is not a general vasodilator but causes vasodilatation, mediated by the vasomotor center and the local nerve supply (69), but the exact mechanism has not been elucidated. Peripheral vasodilatation predisposes to accelerated heat loss. In a cold environment the core temperature declines with a higher rate after alcohol intake compared to controls. The heat loss is also accelerated by later onset of shivering and neglectance of protective measures as the environment is rated warmer after ingestion of alcohol (70). The depressant effect of alcohol on ventilation in humans is also potentiated by lowering of the body temperature (71). An interesting observation, so far only made in experimental animals, is that the elimination rate of alcohol is decreased by hypothermia (72). As the alcohol intoxicated has an increased risk for developing hypothermia, he should be kept warm after an injury, during transport and in preparation for surgery. If possible, infusion solutions and blood should be warmed before administration in order to reduce the increased mortality associated with hypothermia (73).

Alcohol and hemostasis

A normal hemostasis is of vital interest for the traumatized patient. Alcoholism with hepatic cirrhosis is well known to be associated with decreased levels of clotting factors and pathological fibrinolysis (74) while no significant coagulation abnormalities occur in non-cirrhotic alcoholics (75). In the latter group bleeding abnormalities are associated with platelet alterations. The template bleeding time, in patients drinking large amounts of alcohol, increases two-fold despite a normal platelet count (76). In other alcoholics, thrombocytopenia with hemorrhagic manifestations have been reported (77, 78). Alcohol with-drawal results in a rebound thrombocytosis which might contribute to thromboembolic diseases (79). Alcoholism has been associated with decreased platelet production, survival and function (80), but little attention in the literature has been directed to platelet disorders in connection with acute alcohol ingestion in non-alcoholics. Alcohol ingestion results in an increased bleeding time in rats (81) but not in healthy human volunteers (82). Incubation of human platelets with alcohol results in a decreased aggregability (83, 84). Thus, controversy exists over the effects of alcohol on platelet function and the mechanisms behind the demonstrated effects of alcohol remain to be understood.

With millions of people injured or killed while under the influence of alcohol each year, it is surprising to find how limited our knowledge is of how the trauma victim is affected by alcohol. We can conclude that alcohol intoxication interferes with the assessment of CNS and abdominal injuries. Alcohol depresses ventilation and reduces the

resistance to cerebral hypoxia. Alcohol has a cardiodepressant effect and decreases the tolerance to blood loss. It also induces hemoconcentration, acidosis, and increases the likelihood for developing hypothermia. Alcohol also decreases neutrophil mobilization into infected areas. Experimental studies indicate that alcohol might potentiate spinal cord injuries, decrease complement and bactericidal activity of serum as well as RE function. What effect alcohol has on blood is unknown and the effect on platelets controversial with different results obtained in vitro and in vivo. Alcohol intoxicated animals sustain traumatic shock poorly, but the mechanism is unclear. Present knowledge indicates that alcohol intoxication is a negative factor for the victim of trauma, but this has so far not been documented.

SCOPE OF THE PRESENT INVESTIGATION

A critical review of the literature on alcohol and its acute effects on blood, platelets and trauma reactions reveal conflicting results and limited knowledge. In 1973, when this study was initiated, there were only a few studies on acute effects of alcohol on platelets. These studies reported thrombocytopenia after alcohol administration (78, 85) and impairment of collagen but not of ADP induced platelet aggregation in vitro (86, 87). The following discussion will also be based on the information that became available from other groups during progress of the work presented in this dissertation. Conclusions, regarding effects of alcohol on platelet function, have been drawn from studies in which alcohol has been given intravenously (85) or orally (76). Platelet function has been tested in vitro without the presence of other cellular elements of the blood. To extrapolate what happens in vivo from these results is uncertain especially without knowledge of morphological changes that may occur in whole blood exposed to alcohol in vitro and in vivo. In vitro testing of induced platelet aggregation after exposure to alcohol has given conflicting results. One study showed no effect of alcohol (8.7 mM) on ADP induced aggregation (86). Another study (87) demonstrated impairment of collagen but not of ADP induced aggregation after exposure to alcohol (52 mM). Others found that 2 min incubation with alcohol (52 mM) resulted in impairment of collagen and of the second wave of ADP induced aggregation (76). While incubation with alcohol (21 mM) for 4 min had no effect, incubation for 10 min resulted in impairment of ADP induced aggregation (84). At higher alcohol concentration (165 mM) 2 min incubation was followed by impairment of both ADP and collagen induced aggregation (83). These results are summarized in Table I.

Table I. Reported effects of different final alcohol concentrations & incubation times on ADP and collagen induced platelet aggregation.

Author (Ref.)	Alcohol conc. mM	Incubation time min	Impaired aggregation by ADP	Collagen
Zweifler (86)	8.7	?	-	
Quintana (84)	21	4	-	
Quintana (84)	21	10	+	
Davis (87)	52	60	-	+
Haut (76)	52	2	+	+
Stuart (83)	165	2	+	+

These studies reveal that induced platelet aggrgation may be impaired in the presence of alcohol in vitro but the degree of impairment depends on the incubation time, final alcohol concentration and the method for assaying platelet aggregation. Effects of shorter incubation times than 2 min remain to be investigated. There are reports indicating that incubation of platelets with drugs capable of inducing platelet aggregation such as ADP and thrombin, may inhibit platelet aggregation if the final concentration of the drug is not sufficient to induce aggregation (88, 89). This information raises the question whether alcohol, which may inhibit platelet aggregation, also may induce aggregation when added at high concentrations.

All conclusions regarding platelet function in vivo from studies of platelet behavior in plasma can be criticized for disregarding what influence other components of the blood may have. Therefore it seemed increasingly important to study the aggregatin of platelets from whole blood incubated with alcohol which has not been done previously.

There are no reports in the literature of morphological changes in circulating blood following alcohol ingestion. In the present study we demonstrated circulating microaggregates in blood following alcohol ingestion (II). This information brings up the question if these aggregates could be demonstrated and their nature revealed if they were trapped in a capillary bed, e.g., in the liver.

Earlier studies on effects of alcohol on platelets have been focused on platelet aggregation in vitro while the goal must be to gain information of eventual effects in vivo. The finding that platelets play a role in hematogenous metastasis (90) indicated one way of testing platelet function in vivo. Utilizing this biological mechanism, the effects of drugs affecting platelet function, can be tested both after acute and chronic administration of the drug. This method could show if effects of alcohol demonstrated in vitro have any relevance in vivo.

Alcohol affects hemostasis in humans (80) but previously described effects on platelet function require sustained administration and blood levels exceeding 43 mM. A recent study showed a prolongation of the bleeding time and effects on ADP induced platelet aggregation but the changes were not of statistical significance (91). In this study tests were performed two hours after ingestion at an alcohol concentration of 11 mM. Impaired platelet aggregation has been demonstrated in vitro at 22 mM after 10 min of incubation (84). It should therefore be interesting to study bleeding time and platelet aggregation earlier than two hours after ingestion of alcohol and at a higher alcohol concentration. Simultaneous measurement of bleeding time and platelet aggregation is one way to correlate in vivo with in vitro findings.

As pointed out in the introduction a substantial number of patients are traumatized while under the influence of alcohol. Pulmonary

insufficiency is a serious complication to trauma and pulmonary trapping of circulating microaggregates seems to be one etiologic factor (92). We have demonstrated circulating microaggregates after alcohol ingestion (II) and as the impact of alcohol on traumatic shock has never been investigated in respect to circulating microaggregates it seemed interesting to do so and also to study if survival was affected. From the introduction it is understood that the influence of alcohol at the time of trauma should be a negative factor for the patient. On the contrary, a recent retrospective study (93) indicated that the presence of alcohol in the blood on arrival to the emergency room is correlated with a lower mortality than in patients traumatized when sober. No explanation to this positive effect of alcohol was given. It seemed thrilling to challenge this study in a prospective manner.

Based on a critical evaluation of the literature I found it of utmost importance to study:

1. if morphologic changes, by means of microaggregate formation, occur in blood exposed to alcohol in vitro or in vivo

2. if aggregation of platelets in plasma is impaired after incubation with alcohol for 1 min, if alcohol per se can induce platelet aggregation and if platelets, from whole blood incubated with alcohol, show an impaired aggregation

3. if circulating microaggregates, following alcohol ingestion, can be demonstrated histologically and their nature revealed

4. if acute or chronic alcohol ingestion affects hematogenous metastasis

5. if primary hemostasis is affected after alcohol ingestion and if so if it can be correlated to a platelet dysfunction

6. if pre-treatment with alcohol affects circulating microaggregates and survival after traumatic shock

7. if the outcome of severe trauma is affected by the presence of alcohol in the blood at time of injury

MATERIALS

Experimental animals

In rat experiments, inbred male and female Wistar-Furth rats, weighing 170-230 grams, were used. In experiments with rabbits we used male rabbits of Swedish country breed weighing 2.5-4.5 kg. In pig experiments, pigs of Swedish country breed of either sex weighing 16-24 kg were utilized.

Humans

Human volunteers were all healthy men and women who had given their written consent to participate in the study, which was approved by the Ethical Committee at the University of Lund. Intoxicated and non-intoxicated patients were individuals of both sexes sustaining traumatic injuries and admitted to the Trauma Center, San Francisco General Hospital.

Chemicals and drugs

1. Anesthetic drugs. Ether (ACO, Sweden), Thiopentalum (Penthotal®, Abbot, Sweden), Fentanyl (Leptanal®, Leo, Sweden) and Alcuronium chloride (Alloferin®, Roche Sweden).

2. Anticoagulants. ACD solution (ACO, Sweden), Sodium citrate (Becton-Dickinson, France).

3. Alcohol. 99.5 % Ethanol (Vin- och Spritcentralen, Sweden) and whisky (Doctor's Special, Macnish, Glasgow).

4. Platelet aggregating agents. ADP, diluted in 0.15M Trisbuffer solution. Collagen, diluted in isotonic glucose, pH 2.3. ADP and collagen (Sigma Chemical Company, Saint Louis, USA).

5. Radioactive isotope. Xe-133 (Radiochemical Center, Amersham, England).

METHODS

Preparation of platelet-rich and platelet-poor plasma

Four parts of blood was mixed with 1 part of ACD solution. Platelet-rich plasma (PRP) was obtained by centrifugation at 500 x g for 15 min at room temperature. Platelet-poor plasma (PPP) was prepared by centrifugation at 500 x g for 30 min. This method was used in paper I. In papers III and VI blood was mixed with 3.8 % sodium citrate in the proportion 9:1. PRP was obtained by centrifugation at 120 x g for 6 min at room temperature. PPP was prepared by centrifuging the remaining blood at 3 400 x g for 20 min.

Microaggregate determination

Microaggregates were assayed according to the method of Swank (94). Native blood was pumped with a constant speed through a screen with multiple openings 20 μ square. The change in pressure (mm Hg) before the screen was recorded. This Screen Filtration Pressure (SFP) has been demonstrated to correlate with the amounts of microaggregates and depends primarily upon the formation of platelet aggregates. This method was also used to detect aggregates in PRP according to Dhall (95). Details of the equipment are given in paper I.

Platelet aggregation

Platelet aggregation was studied in plasma with the turbidometric method of Born (96). This technique measures continuous change in light transmission through stirred PRP. Adding a platelet aggregating agent results in platelet shape change and aggregation. As the platelets aggregate to each other more lights is transmitted and an aggregation curve can be recorded. As the transmitted light depends on the number of platelets in PRP all tests were performed at a fixed platelet count obtained by mixing PRP with PPP. The tests were performed in an aggregation monitor (Born-Michal Mk IV, Cambridge, England) at 37°C. ADP and collagen were used to induce aggregation. ADP from one frozen stock solution and collagen from one solution stored at 4°C were used throughout each experiment. Platelet aggregation was expressed as rate of aggregation (cm/min) calculated from the increase in light transmission during the first 30 sec. All syringes and test tubes were of plastic materials and the aggregometer cuvettes and stirring bars siliconized.

Indirect measurement of platelet function in vivo

Platelets adhere to circulating tumor cells and metastasis formation is related to platelet-tumor cell interaction (90). Tumors, from rats with a pharmacologically induced colon carcinoma, were incubated with trypsin to obtain a cancer cell suspension. Under light ether anesthesia a laparotomy was performed and the portal vein exposed. The

vein was punctured with a fine needle and 100 000 or 200 000 cancer cells injected into the portal blood stream. The abdomen was closed and anesthesia discontinued. The animals were killed at a later date and the amount of cancer growth taken as a measure of platelet function at the time of cancer cell injection.

Administration of alcohol

Gastric administration was used in all in vivo experiments. Acute administration in rats was performed by giving 4 ml 20 % ethanol by a gastric tube. Prolonged intake of ethanol was accomplished by offering rats a solution to drink consisting of 20 % glucose with an increasing concentration of ethanol from 5 to 20 %, over eight weeks. Pigs were given 500 ml or 15 ml/kg body weight of 40 % ethanol via a gastric tube. In experiments with humans 2 ml/kg body weight whisky (40 % ethanol) was ingested during 15 min after fasting over night.

Liver blood flow measurements

Total liver blood flow was measured with the Xe-133 technique (97). Xe-133 was injected into the portal vein as a bolus and the elimination of Xe-133 from the liver was registered with an external detector. Total liver blood flow was calculated from the initial fast component of the wash-out curve and expressed as ml/min/100 g of liver tissue.

Cardiac output measurements

Cardiac output (CO) was determined with the thermodilution technique (98). A 6F balloon tipped thermistor catheter was introduced into the left jugular vein and its tip placed in the pulmonary artery. By blowing the balloon pulmonary capillary wedge pressure (PCW) was measured. By injecting a cool glucose solution above the thermistor the temperature of blood passing the thermistor was reduced. This temperature change was recorded and from this curve CO calculated by a computer (3520 A, Edwards Laboratories, USA). Each given value for CO was the mean of at least two measurements.

Blood pressure, EKG and temperature measurements

In animal experiments we measured blood pressure in aorta, vena cava and vena porta by introducing large bore polyvinyl-chloride catheters into each vessel. The catheters were connected to transducers (EMT 34, Siemens-Elema, Sweden) which in turn were connected to a recorder (Mingograph 81, Siemens-Elema, Sweden). This recorder was also used for EKG recordings. Rectal temperature was measured by a thermistor (Electrometer, Denmark).

Mechanical ventilation

Pigs under general anesthesia were intubated and mechanically ventilated with a ventilator (LKB, Sweden).

Operative procedures

For in vitro experiments polyethylene or polyvinyl-chloride catheters were inserted, after a small neck incision, in one of the jugular veins of rabbits or pigs. In in vivo experiments with pigs, catheters were placed in vena cava via the left jugular vein and in aorta via the left carotid artery. A midline laparotomy was then performed and by direct puncture a catheter was placed in the portal vein and secured with a purse-string suture. In some animals a second catheter was passed via the left jugular vein to one of the hepatic veins. The position of the catheter was checked by observing the blanchening, of the drained liver parenchyma, following injection of saline via the catheter. Each catheter was passed through the skin and all wounds closed before the experiment started. Histologic specimens were obtained from the liver, as excision or needle biopsies. Some animals were given a soft tissue trauma. This was administered by 200 blows to the inside of each thigh according to Blalock (99). All in vivo experiments ended with an autopsy to check the proper position of each catheter. In traumatized animals it was also checked that the trauma was only to the soft tissue without disruption of major vessels or fractures.

Histologic preparations

Liver specimens were fixed in 2 % glutaraldehyde followed by osmium tetroxide and embedded in Epon. The standard scrutinity of the material was made in 1 µm sections, unstained, stained with toluidine blue or silver-impregnated according to Movat (100). Some of the specimens were processed for electron microscopy in 0.25 µm and 6 000 nm sections, after-stained with lead acetate.

Hematologic tests

Bleeding times were measured by a modification of the template bleeding time (101) using a Simplastic II device (General Diagnostics, Morris Plains, N J). Coagulation was studied with the following parameters. APT-time was counted using a commercial automated method (General Diagnostics, Morris Plains, N J). Factor V was assayed by the method of Wolf as modified by Nilsson (102). Factor VIII according to Nilsson, Blombäck and Ramgren (103). Factor XII by the method of Soulier, Wartelle and Ménaché (104). Prothrombin plus factor VII were determined according to Owren and Aas (105). P & P reagent was prepared by adsorption of bovine plasma with barium sulphate. One stage prothrombin time was measured by a modification of Quick's method using human brain tissue thromboplastin suspension (105). Coagulation time was counted in plastic test tubes according to

Nilsson (102). Recalcification time was determined by mixing citrated plasma with $CaCl_2$ (30 μM, Ferrosan, Malmö, Sweden) without preincubation with silica-containing material. Fibrinolysis was assayed with the following methods. Fibrinogen degradation products (FDP) according to Niléhn (106). Plasminogen was assayed with a direct immunological method (107). Fibrinogen was determined according to Jacobsson as modified by Nilsson and Olow (108). Euglobin clot lysis time and the fibrinolytic activity of plasma and resuspended euglobulin precipitate on unheated bovine fibrin plates (ci-plasma lysed area) were determined according to Nilsson and Olow (108). α_2-macroglobulin was assayed according to Ganrot (109). Antithrombin III by the method of Abildgaard (110).

Hemoglobin was determined photometrically according to van Kampen and Zijlstra (111). Free plasma hemoglobin with the method of Hanks et al (112). Hematocrit with the microhematocrit method (113). Platelets were counted in a Bürkner chamber using a phase-contrast microscope. Serum osmolality was determined with an osmometer (Roebling, Svenska Labex, Stockholm, Sweden). Lactate and puruvate were assayed with commercial methods (Test-Combination Lactate fully enzymatic and Test-Combination Puruvate, Boehringer Mannheim, Mannheim, FRG).

Biochemical tests

Plasma ethanol was determined with gas chromatography as described in paper I. Glucose, lactate, total fat, free fatty acids, ASAT, serum osmolality and acid-base balance were assayed with the standard methods used by the chemical laboratories of the Hospital of Lund and San Francisco General Hospital.

Statistical evaluations

Values are expressed as mean ± SEM. Results were evaluated using the chi-square test, Student's t test for paired and unpaired observations, Mann-Whitney tests, analysis of variance with Bonferroni's t test or Wilcoxon signed rank test (114). The method chosen depended on the experimental design.

COMMENTS ON METHODS

The SFP method

This method, for demonstration of microaggregates in whole blood, has the advantage over other methods, such as electronic particle counting or formalin fixation of aggregates, that no hemolysis of red cells, anticoagulant or centrifugation is needed. The disadvantages are its lack of specificity and the technical problems in performing the test. The pressure that develops in front of the screen depends on the speed by which blood is pumped and the viscosity of the blood. Although viscosity is affected by all formed elements of the blood, SFP has been shown to correspond closely to the size of platelet aggregates (115). An increase in SFP is mainly depending on platelet aggregates as supported by the finding that SFP of whole blood increases with the concentration of added ADP which aggregates platelets (paper I). The viscosity caused by the red cells is of little importance as we found, in another control experiment, that changing Hct from 28 to 38 did not significantly affect SFP (paper II). It has also been demonstrated that increasing the leucocyte count with 40 % does not affect SFP (95). Blood to be tested must be handled uniformly before testing and in order to obtain reproducible results not more than 1 min should be allowed between blood withdrawal and testing. We also noticed that the screen must be secured in the plastic block with an even force. The small test screens should all be taken from the same batch. The blood sampling technique is also critical in order to achieve reproducible results. Any clot or air-bubble in the test syringe will affect the result. Clots and air-bubbles are identified by notches on the pressure recording strip. These problems can be diminished by using shortest possible catheter with a large bore and intermittent flushing of the catheters. Blood was collected in a gravity flow system. The first portion of blood was always discarded.

The turbidometric method

This method, which has been widely used, we considered most appropriate for testing platelet function alone. We chose to express platelet responsiveness to ADP and collagen as aggregation velocity in cm/min, calculated from the increase in light transmission during the first 30 sec. It has been demonstrated that the initial increase in light transmission is directly proportional to the log of the ADP or collagen concentration (116, 117). The time from blood withdrawal to actual performance of aggregation studies is critical (118). We therefore followed a rigorous time schedule and all tests were completed within two hours of blood collection. 3.8 % Sodium citrate was used as anticoagulant and mixed with blood in the proportion of 1:9. This concentration of anticoagulant binds enough calcium, to prevent coagulation during the preparation of PRP, without chelating all plasma calcium as some calcium must be present for normal platelet aggregation to take place (119). Blood was centrifuged at room temperature, all aggregation tests were performed at 37^{o}C, the optimal

temperature for aggregation studies (120). It should be pointed out that the turbidometric method only measures platelet aggregation in stirred plasma. The results obtained in vitro does therefore not necessarily reflect platelet behavior in vivo where other factors such as platelet interaction with red cells (121) or hemodynamic effects (122) may affect platelet function.

Liver blood flow measurements

Liver blood flow can be measured with several methods such as microspheres, pletysmography, thermal and isotope methods (123). We chose the Xe-133 method which is reliable (97) and correlates with other methods (124).

Administration of alcohol

Gastric administration was utilized in all in vivo experiments. We thereby avoided a direct contact between blood and alcohol which occurs with i.v. infusion. A large volume of alcohol was given in order to maintain a high blood alcohol concentration during the experiments. Despite the large volume the resulting blood alcohol level did not exceed 80 mmol/l which is far below the concentration of 150 mmol/l which is considered lethal (125). 40 % alcohol was used as it corresponds to the strongest liquor used in social drinking and gives a rapid increase in blood alcohol levels without causing macroscopic changes in gastric or intestinal mucosa (paper II). In experiments with rats the animals refused to drink solutions containing more than 20 % alcohol.

RESULTS

Alcohol and microaggregate formation in vitro and in vivo (I, II)

Whole blood from pigs or rabbits was mixed with different volumes of 40 % ethanol. SFP of the blood-ethanol mixture increased with increasing final ethanol concentrations (Fig 1).

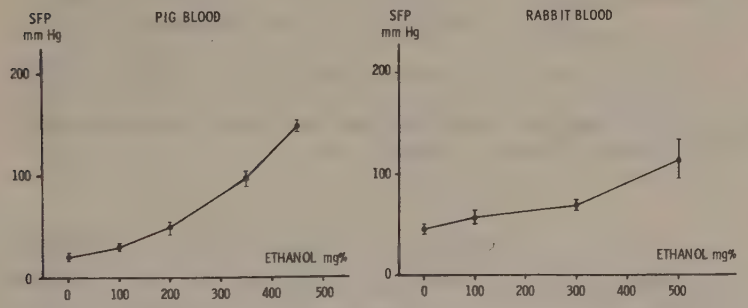
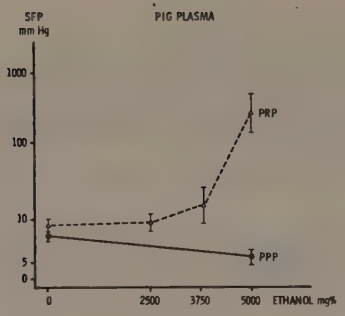


Fig 1 a and b. SFP of pig or rabbit blood mixed with different volumes of 40 % ethanol. Values are mean ± SEM.

Mixing whole blood with saline, in volumes corresponding to those of ethanol added, did not increase SFP. Pig or rabbit PRP was mixed with different volumes of 40 % ethanol. SFP of the PRP-ethanol mixture increased with the final ethanol concentration. Higher concentrations of ethanol were needed to produce an increase in SFP of PRP than were needed to increase SFP of whole blood. The ethanol concentration resulting in an increased SFP of PRP did not increase SFP of PPP (Fig 2).

To investigate if SFP was affected by the presence of alcohol in blood in vivo, pigs were given a single dose each of 40 % ethanol via a gastric tube. As expected, plasma concentrations of alcohol rose with time after alcohol administration. The concentration of alcohol, at a given time, was higher in the portal vein than in vena cava or aorta. With increasing concentrations of alcohol in the blood there was an increase in SFP. In control animals, given saline, SFP did not change (Fig 3).



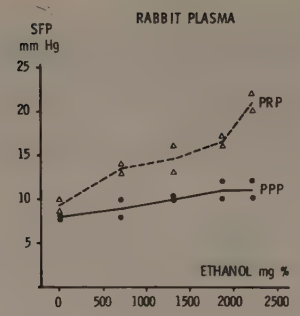
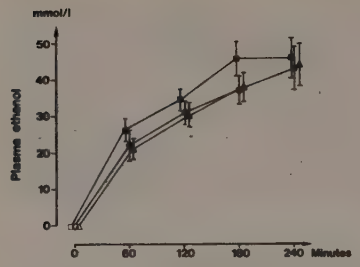


Fig 2 a and b. SFP of pig or rabbit PRP and PPP mixed with different volumes of 40 % ethanol. Values are mean ± SEM.



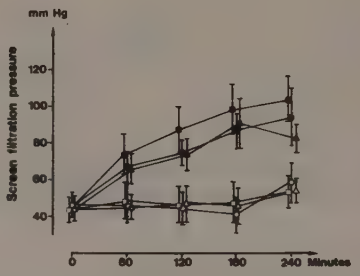


Fig 3 a and b. Ethanol concentration (3a) and SFP (3b) of blood from vena cava (● o), vena porta (■ □) and aorta (▲ Δ) after gastric administration of 500 ml 40 % ethanol (filled symbols) or saline (open symbols). Values are mean ± SEM.

Following alcohol administration, the animals developed a slight hypotension, metabolic acidosis and hemoconcentration. By determining SFP of pig blood with a Hct ranging from 28 to 38 % it was demonstrated that hemoconcentration was not the cause of increased SFP following alcohol administration. The platelet count was unchanged in both groups of animals.

Alcohol and platelet aggregation in vitro and in vivo (III, IV)

The foregoing experiments demonstrated that microaggregates, by means of increased SFP, were formed when a certain concentration of alcohol was reached in whole blood or PRP. No aggregation was found in PPP and platelets were therefore believed to form the aggregates. To investigate if platelets were aggregated when exposed to alcohol we utilized the turbidometric method and SFP. Adding 40 % alcohol to pig PRP resulted in aggregation of platelets, measured with the turbidometric method, at a final ethanol concentration of 630 mmol/l. Aggregation by means of increased SFP was observed at a final alcohol concentration of 820 mmol/l in PRP (Table II).

Table II a and b. Rate of aggregation (IIa) and SFP (IIb) of PRP after addition of 40 % ethanol. The final platelet concentration was kept constant (IIa). Values are mean ± SEM. ** $p < 0.01$; *** $p < 0.001$.

Ethanol mmol/l	Rate of aggr. cm/min
330	0
630	0.14±0.01
1150	0.71±0.01
1650	5.50±0.03
2000	10.00±0.11
2600	34.70±0.88

Ethanol mmol/l	SFP mm Hg
0	21±2
440	24±2
820	51±7**
1500	48±7**
2000	75±4***
2400	273±47***

The aggregation curves were bi-phasic indicating that the platelets underwent a release reaction (Fig 4).

PRP was incubated with different amounts of 40 % ethanol for 1 min. After incubation, at a final ethanol concentration of 175 mmol/l, platelets from the plasma-ethanol mixture demonstrated reduced response to aggregation induced by collagen (Table III). Platelet response to ADP remained unaffected.

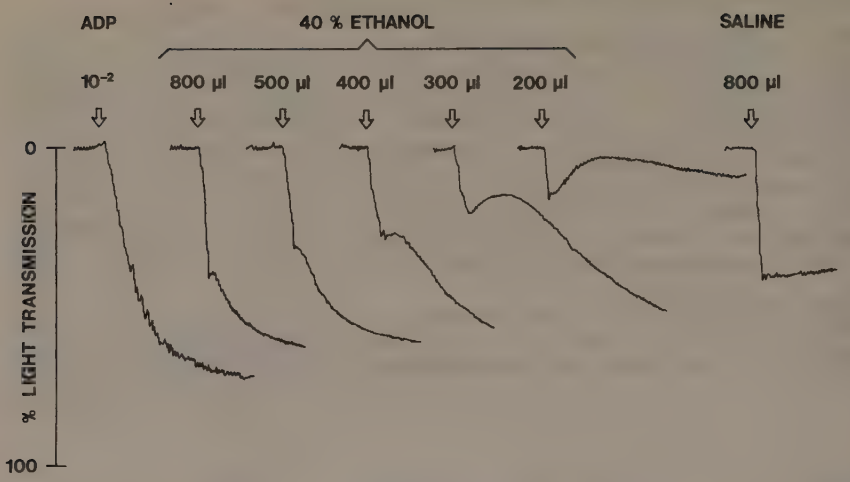


Fig 4. Typical aggregation curves of PRP after addition of ADP, 40 % ethanol or saline.

Table III. Rate of collagen induced aggregation in PRP incubated with corresponding volumes of saline or 40 % ethanol for 1 min. Final collagen concentration was 20 or 40 mg/l. Values are mean ± SEM. * $p < 0.05$; ** $p < 0.01$.

Final ethanol concentration mmol/l	Rate of aggregation cm/min 20 mg/l	40 mg/l
0	8.9 ± 1.3	13.5 ± 1.3
175	5.7 ± 0.9*	8.3 ± 0.8*
0	9.4 ± 0.9	14.2 ± 1.1
350	1.9 ± 0.4**	10.4 ± 2.0

Whole blood anticoagulated with sodium citrate was incubated for 15 min with different volumes of 20 % ethanol. Incubation with 40 % ethanol for 15 min caused hemolysis of the blood. Platelets from alcohol incubated blood, containing 17 mmol/l alcohol or more, had a

decreased response to aggregation induced by both ADP and collagen. Incubating blood with the corresponding volumes of saline did not affect aggregation (Table IV).

Table IV. Rate of collagen and ADP induced aggregation in PRP obtained from blood incubated with 20 % ethanol for 15 min. Final concentrations of aggregating agents were 20 or 40 mg/l collagen and 0.2 or 1.0 µM ADP. Values are mean ± SEM. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Final ethanol concentration	Rate of aggregation, cm/min			
	Collagen		ADP	
mmol/l	20 mg/l	40 mg/l	0.2 µM	1.0 µM
0	14.9 ± 1.4	20.1 ± 1.9	15.2 ± 0.7	21.6 ± 0.7
17	7.6 ± 1.1**	11.5 ± 1.4*	10.1 ± 0.4***	15.5 ± 0.9***
50	6.3 ± 1.3**	10.4 ± 0.9**	13.6 ± 0.9	15.4 ± 0.8***
175	6.5 ± 0.7**	9.0 ± 0.3**	9.5 ± 1.1**	13.2 ± 0.7***
350	1.9 ± 0.3***	4.2 ± 1.1***	9.3 ± 1.1***	10.5 ± 1.0***

These results show that stirred platelets are aggregated by high concentrations of alcohol. Platelets become partly refractory to induced aggregation by unstirred incubation with alcohol in whole blood or plasma. The aggregation of platelets from whole blood incubated with alcohol is affected by 1/10 of the alcohol concentration necessary to induce microaggregates in PRP.

These results indicated that alcohol when added to whole blood or plasma had a direct or indirect effect on platelets. In order to visualize microaggregates, 40 % ethanol as a single dose, was given to pigs. The portal plasma alcohol concentration was 76 mmol/l three hours after alcohol administration. Microscopy of liver biopsies, obtained at this time, revealed large platelet aggregates in low caliber portal venules (Fig 5).

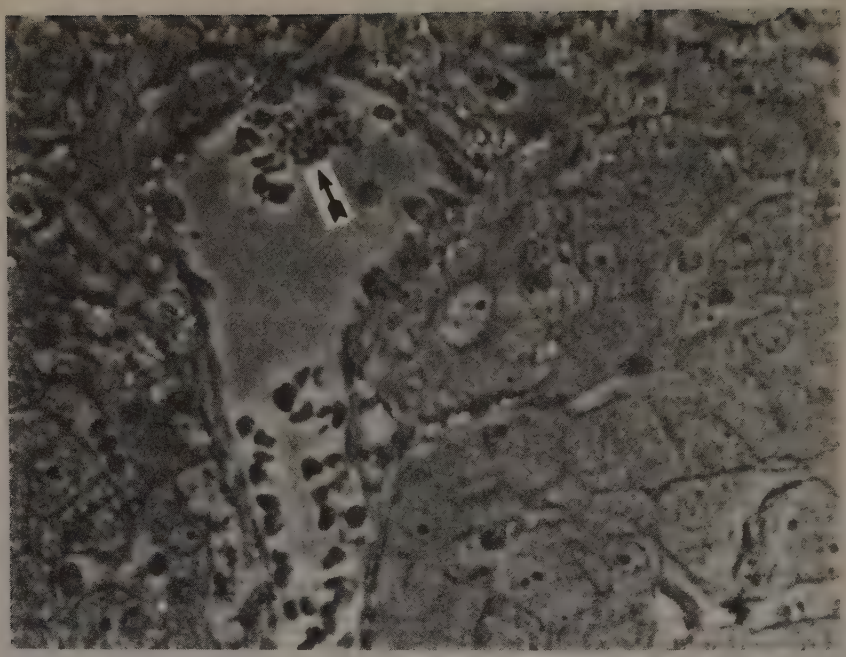


Fig 5. Section of liver biopsy obtained three hours after gastric administration of alcohol. Platelet aggregates were seen in portal venules, see arrow (1 μm section, toluidine blue, x 400).

With increasing blood alcohol levels there was an increase in portal venous blood pressure which remained unchanged in control animals (Fig 6).

Liver blood flow was measured with the Xe-133 technique in order to find an explanation to the increase in portal blood pressure. Three hours after alcohol administration there was a decrease in liver blood flow. This was probably caused by increased hepatic vascular resistance as microscopy from the liver at this time showed marked hepatocyte swelling, narrowing of the sinusoids and platelet aggregates in small portal branches. Following alcohol administration the animals were hypotensive, acidotic, hemoconcentrated and oliguric. Platelet count was unchanged. No changes were observed in control animals given saline.

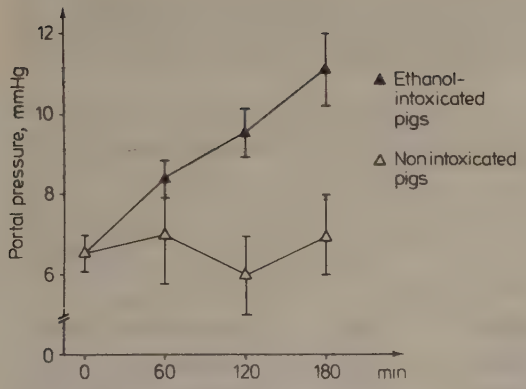


Fig 6. Portal venous blood pressure in pigs after gastric administration of 40 % ethanol or saline at time zero. Values are mean ± SEM.

Alcohol and platelet function in vivo (V, VI)

In rats, the effect of acute or chronic alcohol intake on platelet function was indirectly tested by means of liver metastasis formation after intraportal injection of tumor cells. One hour after acute gastric alcohol administration the plasma concentration of alcohol was 19-21 mmol/l. Intraportal injection of 200 000 cancer cells, at this time, resulted in a higher liver weight than in control animals when sacrificed 13 days later. This means that acute alcohol intoxication enhanced cancer growth in rat livers. The platelet count was reduced 13 days after injection of cancer cells in acutely intoxicated rats (Table V).

Other rats were given glucose solution or glucose-alcohol solution for eight weeks prior to intraportal injection of 100 000 cancer cells. The liver weight and tumor volumes were lower in rats given alcohol than in control animals when sacrificed three weeks after injection of cancer cells. This means that chronic alcohol ingestion reduced cancer growth in rat liver. The platelet count was reduced after eight weeks of alcohol ingestion (Table VI).

Table V. Values of liver weight and platelet count are mean ± SEM, obtained 13 days after intoxication and injection of cancer cells. A1: alcohol intoxicated with cancer cells injected; A2: alcohol intoxicated; A3: non-intoxicated with cancer cells injected; A4: non-intoxicated. * $p < 0.05$; ** $p < 0.025$; *** $p < 0.005$.

Group	No	Liver weight (g)			Platelets x 10^9/l	
A1	9	13.9±0.9	***	***	452± 61	**
A2	4	6.1±0.2			809±158	
A3	9	8.4±0.5	*		727±158	
A4	4	6.2±0.2			715± 9	

Table VI. Values are mean ± SEM, obtained at the start of the experiment (0 weeks), 8 and 11 weeks later. C1 and C2 represent animals fed alcohol/glucose solution and pellets for 8 weeks; then injected intraportally with cancer cells. C3 and C4 represent animals fed glucose solution and pellets for 8 weeks; then injected intraportally with cancer cells. All animals were sacrificed after 11 weeks. * $p < 0.05$; ** $p < 0.025$; *** $p < 0.001$.

Group	No	Liver weight (gm) 11 weeks		Tumor volume (cm^3) 11 weeks		Platelets x 10^9/l 0 weeks	Platelets x 10^9/l 8 weeks	
C1	4	7.3 ± 0.5	**	0.17 ± 0.06	***	810 ± 91	626 ± 39	*
C3	4	9.5 ± 1.1		3.14 ± 1.86		764 ± 41	778 ± 50	
C2	4	12.2 ± 1.4	***	4.31 ± 0.94	***	795 ± 49	626 ± 80	**
C4	4	19.6 ± 1.7		11.44 ± 1.78		723 ± 128	806 ± 36	

Platelet function was also assayed by measuring the template bleeding time in ten healthy volunteers. After fasting over night 2 ml/kg body weight of whisky (40 % alcohol) was ingested during 15 min. One hour after ingestion the plasma alcohol concentration was 19.3 ± 1.6 mmol/l. At this time there was a prolongation of the bleeding time (Table VII) and impairment in platelet responsiveness to both ADP and

collagen (Fig 7 a and b). This impairment of platelet function was also found two hours after alcohol ingestion. Ingestion of this amount of alcohol did not affect parameters of coagulation or fibrinolysis. The data indicate that primary hemostasis is impaired in man after ingestion of moderate amounts of alcohol.

Table VII. Values were obtained before, one and two hours after alcohol ingestion. Values are mean ± SEM. ** $p < 0.02$.

Analysis	Before	One hour	Two hours
Plasma ethanol, mmol/l	0	19.3±1.6	15.5±1.7
Bleeding time, min	7'09±29"	9'34±65"**	8'48±38"**
Osmolality, mosm/l	280±2	304±3**	300±2**
Serum lactate, mmol/l	0.62±0.2	1.45±0.1**	1.11±0.2**
Serum puruvate, mmol/l	23.0±7.1	17.7±2.5	29.3±1.8
Lactate/puruvate ratio	0.028±0.003	0.098±0.002**	0.039±0.006

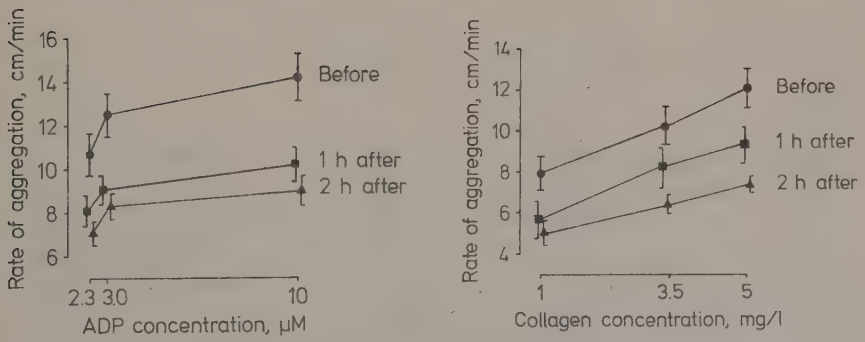


Fig 7 a and b. Rate of platelet aggregation induced by three concentrations of ADP (7 a) or collagen (7 b) before, one and two hours after alcohol ingestion. Values obtained one and two hours after alcohol ingestion were lower ($p < 0.02$) than those obtained before. Values are mean ± SEM.

Alcohol and traumatic shock (VII)

To investigate the impact of alcohol intoxication on traumatic shock, pigs were pre-treated with gastric administration of saline or 40 % alcohol. Following alcohol administration SFP increased in aorta, vena cava and vena porta. Mean plasma alcohol was 63 mmol/l 90 min after alcohol administration. At this time, animals were traumatized with 200 blows to each thigh for two min. One min after trauma CO and MAP had decreased in all animals, while PCW had increased in animals pre-treated with alcohol. Ten minutes after trauma CO and MAP remained low in these animals while saline treated animals were improving.

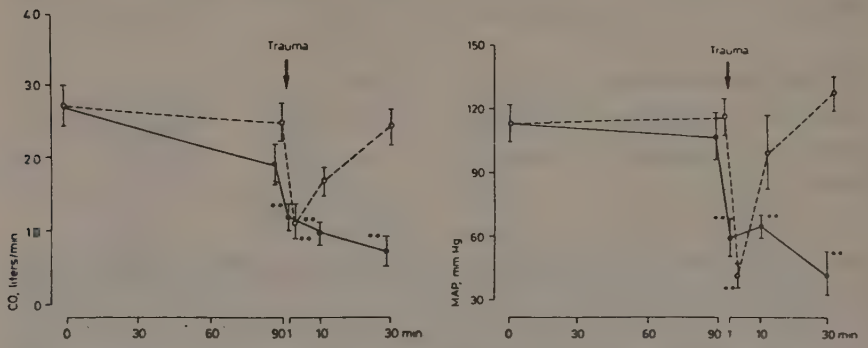


Fig 8 a and b. Cardiac output (CO) and mean artery pressure (MAP) in non-intoxicated (open symbols) and intoxicated (filled symbols) animals, before and after trauma. Values are mean ± SEM. ** $p < 0.01$.

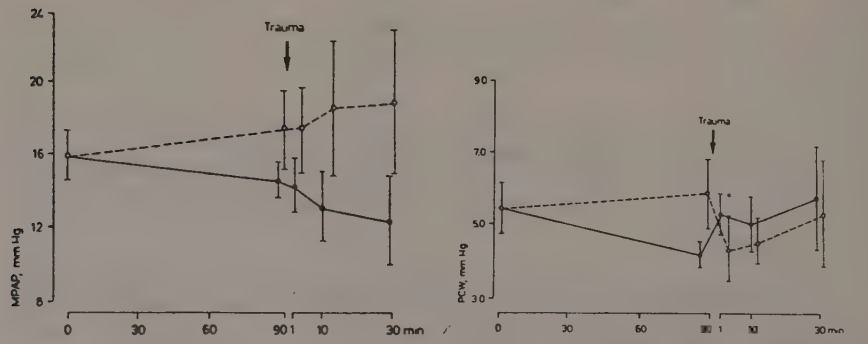


Fig 9a and b. Mean pulmonary artery pressure (MPAP) and pulmonary capillary wedge pressure (PCW) in non-intoxicated (open symbols) and intoxicated (filled symbols) animals, before and after trauma. Values are mean ± SEM. * $p < 0.05$.

Thirty minutes after trauma two alcohol-treated pigs had died while remaining animals in this group had further decreased in CO and MAP. Saline-treated animals were back to pre-trauma levels. No significant changes were seen, during this time period, in PCW or MAP within the two groups but all values for PCW were higher and for MPAP lower in alcohol pre-treated animals compared to controls (Figs 8 a and b, 9 a and b).

From the time of trauma to 30 min after trauma SFP had increased in vena cava and vena porta but not in the aorta in alcohol-treated animals. SFP in vena cava was higher after trauma in control animals. Alcohol-treated animals were acidotic, and had increased lactate and creatinine levels (Table VIII).

Table VIII. Plasma alcohol, SFP, pH, BE, lactate and creatinine, before (0 and 90 min) and 30 min after trauma. Alcohol or saline was given at time zero. Values are mean ± SEM. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

	0 min	90 min	30 min after trauma
Plasma alcohol, mmol/l			
Alcohol treated	0	63±13	72±13
SFP, mm Hg, aorta			
Alcohol treated	27±2	55±3***	47±6
Saline treated	34±1	33±2	33±5
SFP, mm Hg, v. cava			
Alcohol treated	32±3	57±5**	83±17**
Saline treated	31±3	32±4	44±6*
SFP, mm Hg, v. portae			
Alcohol treated	32±3	58±4**	92±10***
Saline treated	36±4	35±2	32±6
pH			
Alcohol treated	7.50±0.05	7.40±0.05	7.23±0.10
Saline treated	7.46±0.02	7.47±0.03	7.41±0.04
BE			
Alcohol treated	2.2±2	-0.5±2	-8.2±2**
Saline treated	3.1±1	2.4±1	0.4±1
Lactate, mmol/l			
Alcohol treated	2.0±0.3	3.2±0.5	6.2±0.6**
Saline treated	1.1±0.9	1.0±0.1	2.4±0.6
Creatinine, mmol/l			
Alcohol treated	86±7	95±5	120±5**
Saline treated	83±9	78±6	97±7

In the experimental period, 30-150 min after trauma 4 out of 5 surviving animals given alcohol died. This occurred 35, 40, 50 and 65 min after trauma. No control animals died.

These data indicate that alcohol intoxication decreases survival after traumatic shock and that both alcohol and trauma induces a significant increase in circulating microaggregates.

Alcohol and outcome of severe trauma (VIII)

To investigate if presence of alcohol in the blood, in seriously injured non-alcoholics, affected morbidity or mortality a prospective study was undertaken. Sixty-nine patients fulfilled the requirements to enter the study. Thirty-five patients were found to have alcohol in the blood. Mean alcohol concentration was 136 ± 13 mg/100 ml. The two groups did not differ regarding age, sex, injury mechanisms or regions injured. Mean Injury Severity Scores (ISS) were not statistically different. Patients with alcohol in the blood presented themselves in the emergency room with lower blood pressure and PCO_2 values than the rest of the patients (Table IX).

Table IX. ISS, BP, pulse rate, Hb, Hct, PCO_2, pH and BE on arrival in the emergency room. Values are tabulated for patients with or without alcohol in the blood.

Values on arrival	Alcohol	Control	p-value
ISS	24.3±2.4	25.7±2.0	N.S.
BP, mm Hg	92.9±4.4	108.2±4.3	< 0.05
Pulse rate/min	103.5±2.8	104.3±3.0	N.S.
Hb, g/100 ml	13.3±0.4	13.0±0.5	N.S.
Hct, %	38.4±1.2	36.5±1.3	N.S.
PCO_2, mm Hg	33.3±1.6	38.7±1.9	< 0.02
pH	7.28±0.02	7.26±0.02	N.S.
BE, mmol/l	-9.1±1.4	-8.2±1.8	N.S.

The hospital course was the same for both groups of patients. The over all mortality was low (4.3 %) and did not differ between the two groups (Table X).

Table X. Hospital course and mortality in patients admitted with or without alcohol in the blood.

Hospital course	Alcohol	Control	p-value
Admission-OR, min	108±18	109±20	N.S.
OP-time, min	160±18	157±14	N.S.
ICU-stay, days	3.3±0.9	4.9±1.3	N.S.
Tot. par. nutr., days	5.9±1.3	5.8±0.8	N.S.
Temp > 100°F, days	5.7±1.1	5.8±1.2	N.S.
Hosp.-stay, days	15.7±3.3	16.5±2.4	N.S.
Mortality, n	1	2	N.S.

DISCUSSION

The development of post-traumatic respiratory failure correlates with a high mortality (126). This complication has been associated with pulmonary entrapment of microaggregates and platelets (92, 127). One possible mechanism is platelet aggregation induced by increased levels of free fatty acids (128) found in blood after major trauma (129). To study if microaggregates could be induced by fatty acids in vitro, fatty acids dissolved in alcohol were added to pig or rabbit blood. Dissolved fatty acids and surprisingly alcohol alone caused an increase in Screen Filtration Pressure (SFP) of blood. This was the incentive to investigate effects of alcohol on blood.

Interest was focused on circulating microaggregates in blood and especially on platelet aggregation. Normally platelets circulate in the blood as round disc-shaped cells that do not adhere to each other. Exposed to broken endothelium or a variety of artificial surfaces platelets adhere to these surfaces and undergo a number of internal changes. This eventually results in their adhesion to each other, they aggregate. Although the mechanisms are still poorly understood, ADP appears to play a central role. ADP is capable of directly aggregating platelets. ADP is present in high concentrations in platelets and when platelets are stimulated by different substances this endogenous ADP is released from platelets resulting in their aggregation. Prostaglandins play an important role in mediating this platelet release reaction. Platelet aggregation by ADP is associated with activation of membrane phospholipase to yield arachidonic acid. This is in turn converted to thromboxane A_2 with the capacity of aggregating platelets and inducing the release reaction. Thromboxane A_2 mediated release is probably important only at low concentrations of aggregating agents (130). ADP and collagen, in different concentrations, were chosen as aggregating agents in this study. ADP may cause a double wave of aggregation; the first wave is due to a direct effect of ADP and the second to thromboxane A_2 synthesis and release of endogenous ADP. Collagen, on the other hand results, after a lag period, in a single wave of aggregation as the result of thromboxane A_2 and ADP release from platelets. In vivo, platelets are responsible for primary hemostasis. When the endothelium is broken, platelets adhere to collagen and are aggregated which results in the formation of the platelet plug, largely responsible for the primary arrest of bleeding. This mechanism is disturbed by drugs inhibiting platelet aggregation such as aspirin and indomethacin (131). This study indicates that also ethanol affects platelet function.

Before discussing the results, the hazards of extrapolating results from animal experiments to humans should be emphasized. This is especially true for platelet studies in vitro. Citrated human, pig, rabbit and rat platelets aggregate in the presence of ADP (132, 133, 134). Human platelets are the most sensitive. ADP induced secondary aggregation occurs in citrated human platelets but not in citrated rat, rabbit and pig platelets (134) or human platelets in a medium

with physiologic concentrations of calcium and magnesium (135). This demonstrates the difficulties in comparing platelet aggregation in vivo and in vitro and between species. Response to collagen occurs reliable across species boundaries (133). ADP, thrombin and collagen cause release of adenine nucleotides in human PRP but to a much less extent in rabbit and pig PRP. Washed rabbit and pig platelets, however, behave like human platelets, demonstrating that the method for preparation of platelets makes a considerable difference to the responses obtained in vitro (136). The fact that both serotonin (137) and platelet factor 4 (138) are released from rabbit platelets in vivo suggests that the platelet release reaction occurs more readily when the level of ionized calcium is optimal. Thus, the absence of a reaction in vitro does not mean that it does not occur in vivo.

Alcohol and microaggregate formation (I, II)

Adding alcohol to native blood from pigs or rabbits in vitro, resulted in formation of microaggregates as indicated by an increased SFP. This occurred at an alcohol concentration of 44-66 mmol/l. It is unknown whether smaller aggregates were formed at lower concentrations of alcohol. With the SFP method, aggregates must exceed a critical diameter of approximately 50 μ before there exists a correlation between aggregate size and SFP (95). Another problem with the method is that it does not tell what actually causes the increase in SFP. SFP is not affected by red cell aggregation or leucocyte stickiness (95). It is also unlikely that the increased SFP resulted from precipitation of denaturated proteins on the screen, as SFP of PPP was unaffected by addition of up to 10 times the concentration of alcohol that increased SFP of whole blood. Adding the corresponding amount of alcohol to PRP resulted in an increased SFP. This suggests that the increase in SFP was caused by aggregated platelets. The difference in alcohol concentration necessary to increase SFP in whole blood and PRP can be explained in two ways. First, in PRP platelets are the only cells to form aggregates and occlude the screen. The number and/or size of aggregates must therefore be larger in PRP than in blood, where a mixture of aggregates, red and white cells more easily can partially block the flow through the screen. A drawing describes this hypothesis (Fig 10). Secondly, alcohol might affect other cells than the platelets to release platelet aggregating substances. One such substance is ADP which the red cells contain in large amounts (139). Alcohol exerts a fluidizing effect on erythrocyte cell membranes (140) and exposure of red cells to alcohol might result in release of ADP resulting in aggregation of platelets. This mechanism is supported by the recent finding that platelets are aggregated by low concentrations of ADP, 0.1 μM, leaking from erythrocytes, when the calcium concentration is physiological (141). The calcium concentration was assumed to be physiologic in the present experiment as no anticoagulant was added and the tests performed within one minute of blood withdrawal.

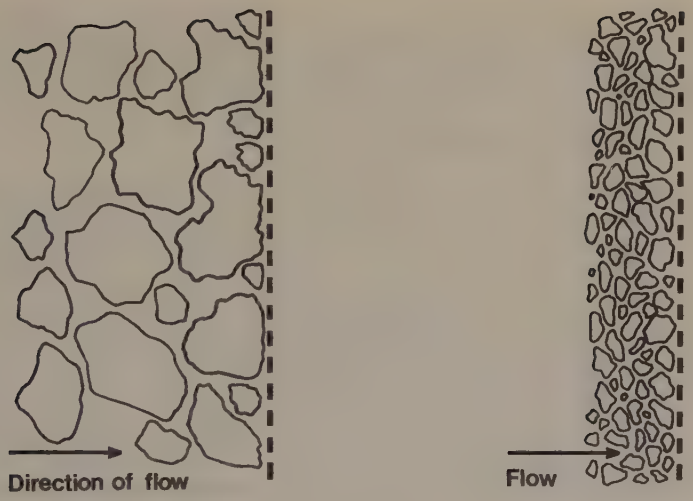


Fig 10 a and b. Hypothetical build-up of aggregates in PRP (10 a) and of aggregates, red and white cells in whole blood (10 b) in front of the filtering screen.

To investigate if microaggregates were formed by alcohol in vivo, alcohol was given by the gastric route to pigs. Pigs were chosen because of the in vitro observation with pig blood and because pigs do have a blood volume which allows repeated measurements of SFP without producing a blood loss that might affect the platelets (142, 143). Microaggregates, by means of increased SFP, were found one hour after alcohol administration. At this time the alcohol concentration was 18-30 mmol/l. SFP continued to rise with increasing alcohol concentration. Gastric administration of saline did not affect SFP. With increasing alcohol concentrations there was also an increase in hematocrit. By SFP determination of blood with different hematocrit, it was demonstrated that hemoconcentration was not the cause of the increased SFP. The concept that the microaggregates were made up by platelets was not supported by a decrease in circulating platelets. One explanation is that aggregation might be reversible and of short duration, allowing disaggregation while blood is prepared for platelet counting. This is in concordance with the observation in vitro that ADP induced aggregates of citrated pig platelets easily disaggregate (144). Another explanation is that these animals were not splenectomized and pooled platelets might have been released. This has been demonstrated in animals after pulmonary trapping of labelled patelets (145). The in vitro results suggested a direct effect of alcohol on platelets and an indirect effect via red cells. This study suggests that a third mechanism might be involved in vivo as intoxicated animals developed metabolic acidosis. Acidosis at a pH of

7.2 has been demonstrated to trigger intravascular coagulation (146) which could affect SFP. However, no animal was acidotic to this extent, and SFP increased before pH was markedly decreased. Acidosis therefore seems unlikely to have affected SFP.

Alcohol and platelet aggregation (III, IV)

The observation that alcohol may act as a platelet release inducer (147) suggests that alcohol may affect platelets to release ADP. Release of endogenous ADP is necessary for secondary aggregation of platelets (148). This only occurs above 30°C (149), indicating that membrane fluidity is of importance for the release reaction. Alcohol exerts a dose related fluidizing effect on lipid containing cell membranes (150) which is a possible mechanism for the effect of alcohol on platelets. As the membrane effect of alcohol is dose related, the effect of alcohol on platelets depends on the final alcohol concentration. This is in concordance with the present results. Platelets were aggregated at a final alcohol concentration of 630 mmol/l. With a further increase in alcohol concentration there was an increase in aggregation velocity. Short incubation of pig PRP with alcohol, 175 mmol/l, resulted in an impaired aggregation when collagen was added. The impairment was greater at a higher alcohol concentration. This negative dose related effect of alcohol on collagen induced aggregation can be explained by the same mechanism. Collagen induced platelet aggregation is mediated by release of endogenous ADP (151). These amounts of alcohol may have induced platelet release of ADP, insufficient to induce aggregation in citrated plasma, resulting in a decreased intracellular ADP and reduced ability to aggregate upon exposure to collagen. These results are in concordance with those of others who have demonstrated that the first noticible effect on human platelets incubated with alcohol is a reduction of secondary aggregation induced by ADP (84) and impairment of collagen induced aggregation (83).

Both ADP and collagen induced aggregation in pig PRP, from citrated blood incubated with alcohol, was impaired as related to the final alcohol concentration. Impaired aggregation was seen after 15 min incubation at 17 mmol/l. The fact that aggregation was impaired at a tenth of the alcohol concentration that impaired aggregation in PRP can be explained by the increased incubation time. Platelet release of ADP may not only result in a decreased level of intracellular ADP but also in platelet refractoriness as a consequence of increased extracellular ADP. Platelets exposed to ADP without stirring, become refractory to ADP induced aggregation, and platelets that have aggregated and deaggregated under the influence of ADP are refractory to further addition of ADP (152). This could mean that prolonged incubation of citrated blood with alcohol results in impairment of ADP induced aggregation due to refractoriness while collagen induced aggregation is impaired due to reduced platelet ADP. Regardless of the incubation time, this study also demonstrates that when blood was incubated with alcohol, only one tenth of the alcohol concentration

was needed to affect platelet function compared to incubation of PRP. This suggests, once more, that the red cells might be involved. This concept is supported by the observation that 40 % alcohol caused hemolysis and although no detectable hemolysis occurred when 20 % alcohol was added, ADP can have been released from red cells without concomitant hemolysis (153, 154). The importance of red cell interaction with platelets for a normal platelet function has recently been re-established (155). Release of ADP from red cells may have contributed to platelet refractoriness in unstirred blood, while causing platelet aggregation in stirred blood, in concordance with the results in paper I.

Three hours after gastric administration of alcohol, large platelet aggregates were demonstrated in liver biopsies. The blood alcohol concentration was 76 mmol/l when the biopsies were taken. The demonstration of large platelet aggregates correlates with the increase found in SFP of pig blood in vitro and in vivo at the corresponding alcohol concentration, and supports the hypothesis that platelets are aggregated by alcohol in blood in motion. An interesting observation was the acute increase in portal pressure following gastric administration of alcohol. This was also found in an unpublished observation of 2 patients with portal catheters who were given alcohol to drink (156). In the present study, the increased pressure was probably due to increased hepatic vascular resistance. A decreased total liver blood flow and narrowing of the sinusoids, a consequence of hepatocyte swelling, was demonstrated. This observation might explain the clinical observation that bleeding from oesophageal varices in cirrhotic patients is often seen during a period of heavy drinking. An increased portal pressure might also increase the risk for severe intra-abdominal bleeding in patients traumatized while under the influence of alcohol.

Alcohol and platelet function (V, VI)

Trauma increases platelet reactivity (142, 157, 158). Increased platelet reactivity after trauma is associated with increased metastasis formation after injection of tumor cells in the rat (159). Conversely, thrombocytopenia impairs the development of metastases after injection with tumor cells (160). Platelet aggregating material (PAM) has recently been isolated from the cell surface of rat tumor cells (90). This implies a direct role for the platelet in the pathogenesis of tumor cell metastases. The hypothesis that platelet stimulation with alcohol would enhance cancer growth was tested in rats. Animals pre-treated with gastric administration of alcohol had a plasma alcohol level of approximately 20 mmol/l one hour later. Intraportal injection of cancer cells, at this time, was associated with enhanced liver metastasis formation. This was found 13 days after injection, when the animals were killed and the livers compared to livers in the control group. Rats were used as they were utilized in earlier studies on platelets and metastasis formation. The limited blood volume precluded SFP determinations. The enhanced cancer growth

in rat liver may be the result of alcohol on platelets making the platelets more aggregable, thereby favoring platelet tumor cell interaction. These results are unlikely to be the consequence of increased hepatic vascular resistance, as demonstrated in pigs after alcohol ingestion because portal blood flow is increased after alcohol ingestion in the rat (81).

Feeding rats an alcohol-glucose solution for eight weeks, resulted in thrombocytopenia. The thrombocytopenic effect of alcohol has in man been attributed to a direct toxic effect of alcohol (79), which is consistent with the rebound thrombocytosis seen after alcohol withdrawal. The mechanism is unknown but a decreased platelet life span has been demonstrated (161). Portal injection of cancer cells in rats, made thrombocytopenic by alcohol ingestion, resulted in liver metastasis formation. This was observed when the rats were sacrificed three weeks later. There was less cancer growth than in control rats. This was in concordance with previous results (160). The present results may be caused by the reduced number of platelets or of an impaired platelet function which has been demonstrated in man after prolonged alcohol intake (76). These results indicate that platelet function is affected by alcohol ingestion in rats.

Platelet function is also affected by acute alcohol ingestion in man. One and two hours after ingestion, at a mean alcohol level of 19 and 16 mmol/l, the template bleeding time was prolonged. Platelet aggregation by ADP or collagen was impaired simultaneously. The impairment was greater with collagen. In vitro, incubation of human PRP with alcohol, 21 mmol/l, for 10 min results in a slight reduction in maximal aggregation induced by ADP (84). In another study, incubation of PRP, at the same alcohol concentration, for 2 min did not affect ADP or collagen induced aggregation (83). The demonstrated more pronounced effect of alcohol in vivo on platelet aggregation, at the corresponding alcohol concentration, might be explained by prolonged exposure of platelets to alcohol, or by an indirect effect of alcohol on platelets. The demonstrated fluidizing effect of alcohol on lipid containing cell membranes, which is dose dependent (150) may affect both platelets and red cells. Alcohol may by increasing fluidity in platelet membranes, possibly induce shifts of internal platelet calcium and induce the release reaction. Degranulation of human platelets in the absence of aggregation has recently been demonstrated (162). When these platelets are tested in vitro an impairment of the second phase of ADP and of collagen induced aggregation could be explained by the reduced granule storage pool (163). Red cells exposed to alcohol in vivo may leak ADP resulting in platelet refractoriness or aggregation. A refractory state of platelets has been observed following major surgery and was believed to be due to liberated ADP (164). Released ADP may also have induced aggregation and sequestration of the most aggregable platelets of the heterogenous circulating platelet pool (165, 166), leaving the less aggregable platelets to be tested. Seemingly conflicting results are given in a recent study reporting no response of platelet aggregation

or bleeding time to alcohol two hours after ingestion (91). Despite the different conclusions in this and the present study there is a tendency towards similar results in the two studies. The earlier study demonstrated a prolongation of the bleeding time two and four hours after alcohol ingestion and minimal effects on platelet aggregation in vitro but the changes were not statistically significant. These effects of alcohol were demonstrated to be of statistical significance in the present study. This was probably due to higher alcohol concentrations, shorter interval between ingestion and testing and a different method for assaying platelet function in vitro. Our subjects ingested a somewhat larger dose of alcohol and were fasting before ingesting alcohol which favors rapid resorption (167). We measured the bleeding time already one hour after ingestion and the time factor is probably important because the prolongation of the bleeding time was less pronounced after two hours and we know from animal experiments that the bleeding time is normalized four hours after ingestion (81). In the present study we used aggregation velocity to assess platelet responsiveness. This method is more sensitive in assaying platelet responsiveness than measuring maximum aggregation (117). The demonstrated reduction in platelet responsiveness may explain the prolongation of the template bleeding time observed after alcohol ingestion. These results imply that alcohol ingestion, with alcohol levels below those considered illegal for motorists in most countries, increases the risk for a severe bleeding after trauma.

Alcohol and traumatic shock (VII)

Ninety minutes after gastric administration of alcohol to pigs, circulating microaggregates were found in the blood. Soft tissue trauma, at this time, induced a state of shock with a decreased cardiac output and mean arterial blood pressure. The number of circulating microaggregates, induced by alcohol and trauma, was reduced after passage over the lungs. This was probably caused by the state of shock, which may induce a decrease in pulmonary capillary circulation. This mechanism seems to be regulated by neural pathways as it can be abolished by denervation of the lung (168). Pulmonary trapping of microaggregates was also indicated by the increase observed in pulmonary capillary wedge pressure after trauma to intoxicated animals. Trauma to non-intoxicated animals induced microaggregates in vena caval blood. No aggregates were found in aortic blood of these animals indicating that the aggregates were trapped in the lung. These results imply that acute alcohol intoxication may increase the filtering burden of the lungs. If this occurs in humans it might increase the risk of developing post-traumatic respiratory insufficiency which has been associated with pulmonary microaggregate trapping (92, 127).

A most striking observation in this study was the inability of intoxicated animals to sustain traumatic shock. Six out of seven intoxicated animals died within 65 min of the trauma while no traumatized control animal died. The mortality was associated with

difficulties to restore circulating volume after trauma which is in concordance with other observations that intoxicated animals and humans have less tolerance to blood loss (60, 61, 64, 66). There are several possible mechanisms by which alcohol may aggrevate hypovolemia. Alcohol is a peripheral vasodilator (169), vasodilation can induce a relative hypovolemia. This is probably less important in this study as the core temperature did not change. Alcohol ingestion has been associated with an increased bleeding tendency in rats (81) and humans (Paper VI). This mechanism seems relatively unimportant in this study as no differences were found in extravasation of blood at the trauma sites at macroscopic comparison between intoxicated and control animals. The observations that alcohol ingestion increases hepatic vascular resistance in pigs (Paper IV) and dogs seem to be of greater importance (170). This may result in pooling of splanchnic blood which becomes relatively unavailable to the traumatized intoxicated animal. All animals were under general anesthesia which reduces the sympathetic discharge following trauma and increases the drop in blood pressure following hemorrhage in the pig (171). Alcohol may, however, counteract the effects of general anesthesia by increasing catecholamine turnover in both central and peripheral tissues, independent of sympathetic discharge (172). It is therefore difficult to evaluate the effects of anesthesia on the circulatory changes after trauma in alcohol intoxicated animals. For ethical reasons these experiments could not be carried out in non-anestetized animals. If traumatized alcohol intoxicated humans react as the animals in this study, it underlines the importance of rapid and adequate fluid resuscitation in these patients.

Impact of alcohol in severely injured patients (VIII)

We have demonstrated impairment of primary hemostasis in healthy volunteers (Paper VI) and a reduced ability to sustain traumatic shock in pigs (Paper VII) after acute alcohol ingestion. These results were the incentives to study bleeding, morbidity and mortality in severely traumatized non-alcoholics under the acute influence of alcohol. Severely injured patients, with non-neurologic injuries, were randomized into two groups based on presence or absence of alcohol in the blood on admission to the hospital. The study was prospective and therefore patients with chronic alcoholism, barbiturates in the blood, serious concurrent illness or anticoagulant therapy could be excluded in order to get a homogenous composition of the two groups. Alcohol was found to be present in half of the patients (51 %). This figure seems high but this result corresponds with figures from other metropolitan emergency rooms (173, 174). The two groups did not differ regarding pre-hospital parameters, including age, type and severity of injury. The patients were brought to the hospital half an hour after injury. When presenting in the emergency room patients with alcohol in the blood had a more pronounced hypovolemia than patients with negative blood alcohol tests. This hypovolemia could, however, not be explained by an increased bleeding in patients traumatized while under the influence of alcohol. This, because other parameters such as Hb,

Hct, pulse rate or fluids given during the first 24 h, did not differ significantly. Hypovolemia was therefore attributed to depressed myocardial function which follows ingestion of alcohol in normal subjects (55). Traumatized patients were acidotic on arrival in the hospital. Patients with alcohol in the blood had a lower mean PCO_2 value than the other patients. This was believed to be due to hyperventilation induced by the metabolic acidosis which results from the metabolism of alcohol (68). The mortality was very low (4.3 %) in relation to the mean Injury Severity Score (ISS) of 25. At this ISS a mortality of 16 % and an average hospital stay of 16 days should have been expected (175). This length of hospital stay corresponds to what was found in the present study while the unexpected low mortality rate could be referred to unusually good surgical treatment. This favorable outcome of trauma could to some extent be attributed to the exclusion of neurologic injuries and to a short-time interval between injury and definitive treatment. At a longer pre-hospital time, which is usually seen in more rural areas, the outcome could have been less favorable as a consequence of metabolic and cardiogenic effects of alcohol.

SUMMARY

1. Alcohol induces formation of microaggregates in pig and rabbit blood and plasma in vitro.

2. Gastric administration of alcohol induces formation of circulating microaggregates in pigs.

3. Alcohol causes aggregation in pig platelets in plasma. The aggregation curves indicate that alcohol induces platelet release. Incubation of pig plasma and blood results in impairment of induced platelet aggregation.

4. Large platelet aggregates are found in liver biopsies from pigs after gastric alcohol administration. This also induces acute portal hypertension.

5. Acute gastric alcohol administration enhances and eight weeks pre-treatment with oral alcohol reduces the development of metastases in rat liver after intraportal injection of tumor cell.

6. Ingestion of whisky, resulting in low to moderate blood alcohol levels in healthy volunteers, is associated with an increased bleeding time and impairment of platelet aggregation tested in vitro.

7. Traumatic shock in pigs pre-treated with alcohol results in a decrease of circulating microaggregates over the lung and a high mortality.

8. Presence of alcohol in the blood, on arrival in a trauma center 30 min after severe non-neurologic trauma, does not affect the mortality rate in non-alcoholics compared to patients with negative alcohol tests. Alcohol in the blood on admission is correlated to a low blood pressure and PCO_2 value.

GENERAL CONCLUSIONS

Both addition of alcohol to pig blood in vitro and gastric administration of alcohol to pigs result in formation of microaggregates in the blood at moderate alcohol concentrations. These microaggregates are probably made up by aggregated platelets because when circulating microaggregates are demonstrated in the blood large platelet aggregates are shown histologically in small portal branches. By a ten-fold increase of the alcohol concentration, which induces microaggregates in whole blood, microaggregates can be identified in platelet rich plasma (PRP) and platelets shown to aggregate. The curves registered while platelets aggregate indicate that alcohol may act as a dose depending platelet release inducer. This means that alcohol may induce release of ADP stored in granulae in the platelets which, if the dose of the release inducer is sufficient, results in aggregation of the platelets. This conception is supported by the finding that platelets after incubation with alcohol in plasma, at concentrations insufficient to induce platelet aggregation, show an impaired aggregation after addition of collagen. This reaction is depending on a rather momentary release of platelet ADP. The mechanism is probably that alcohol like other release inducers such as ADP, when added in a concentration insufficient to induce platelet aggregation, brings the platelets into a refractory state as a consequence of leakage of intra-platelet ADP.

Platelets seem to be approximately ten times more sensitive to the effects of alcohol in blood compared to plasma. This idea is based on observations regarding alcohol concentrations necessary to induce microaggregates in blood or in plasma as well as refractory platelets in blood or in plasma. The author has not proved but believes that this difference depends on the presence of red cells in the blood. A fluidizing effect of alcohol on red cell membranes has been demonstrated by others. Red cells contain most of the ADP of blood and the increased sensitivity of platelets to alcohol in blood can be the result of a combined effect of alcohol on platelets directly and indirectly due to release of ADP from red cells.

Platelets play a role in hematogenous metastasis. The effect of alcohol on platelet function in this respect was studied in rats. Alcohol given orally as an acute dose enhanced and chronic administration of alcohol reduced liver metastasis after intraportal injection of cancer cells, indicating that platelet function was affected. Platelet Aggregating Material (PAM), recently isolated from the surface of tumor cells, causes platelets to aggregate with the tumor cell. Thereby the nidation of the tumor cell, to the wall of the vessel, facilitates. The explanation to the enhanced take of circulating tumor cells, when alcohol is given acutely, is probably that alcohol affects both platelets and red cells to release ADP which acts synergistically with platelet aggregating PAM. Prolonged administration of alcohol renders the platelets refractory so they respond less to PAM, resulting in a reduced take of circulating tumor cells.

In man, following ingestion of small to moderate amounts, alcohol impairs primary hemostasis. The bleeding time is prolonged and associated with an impaired platelet aggregation. The mechanism is believed to be the same as demonstrated in animals after alcohol ingestion, e.g., that platelets exposed to low concentrations of alcohol become refractory.

Alcohol is often a genesis for trauma and present in the blood of its victims. Alcohol pre-treated pigs demonstrate a decreased resistance to traumatic shock resulting from an inability to restore circulation after trauma. Soft tissue trauma to these animals increases the circulating microaggregate burden on these animals and results in 86 % mortality compared to no mortality in controls. Anesthesia may have influenced these results but they indicate that alcohol may be a negative factor for victims of trauma. A prospective study of severely injured patients confirm that alcohol in the blood on arrival in the hospital is related to a reduced blood pressure. As a result of the short duration between trauma and treatment no pronounced differences in the severity of traumatic shock or in metabolic dearrangements had had time to be established. That is why, as expected, no differences were found regarding morbidity or mortality.

It is thus established that platelet function is affected in the presence of alcohol in the blood. This may be of importance in clinical conditions where platelet function is involved such as ischemic heart disease, hematogenous metastasis and bleeding. Alcohol affects hemodynamics after trauma. Surgeons should therefore first be aware of the high frequency of trauma victims with alcohol in the blood, and secondly be aware of that these patients need a more aggressive shock treatment which to some extent depends on the time spent between injury and treatment.

ACKNOWLEDGEMENTS

To all, who have contributed to this study, I want to express my sincere thanks.

The fiscal support provided by the Medical Faculty of the University of Lund, Pharmacia, Maggie Stephens' Foundation, Swedish Medical Research Council (SMRC, grant no B82-17R-6191) and Swedish Cancer Society (SCS), is gratefully acknowledged.

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PRINTING
ILLUSTRATION DEPARTMENT
DEPARTMENT OF SURGERY
UNIVERSITY OF LUND
1983.